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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/518,955	QIAN ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *8,9,11-18 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,10 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Upon review, claims 8 and 9 should not have been included in Group I because they are directed toward a knock-in non-human animal, i.e. a transgenic mouse lacking a functional mouse AgRP gene that expresses a non-native AgRP protein, e.g. human AgRP. Group I, claims 1-7, 10 and 19, is limited to a knockout non-human animal and is patentably distinct from Group II, claims 8 and 9, because a knockout non-human animal has a different structure and function than a knock-in non-human animal for reasons of record.

Applicant's election with traverse of Group I, claims 1-10 and 19 in the reply filed on 9-11-06 is acknowledged. Because of the inadvertent error in the list of claims in Group I, applicants' election is limited to claims 1-7, 10 and 19.

The traversal is on the ground(s) that examination of all the knockout non-human transgenic animals (Group I) and knock-in nonhuman animals (Group III) as a single invention will not impose a burden on the Examiner that differs significantly from the burden of examining Group I alone. This is not found persuasive because the claims drawn to knock-in animals would require additional searches, additional art rejections and additional considerations under enablement. The animals in Groups I and III have a different structure and different function and are considered patentably distinct.

The requirement is still deemed proper and is therefore made FINAL.

Claims 8, 9, 11-18 and 20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable

generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 9-11-06.

Claims 1-7, 10 and 19 are under consideration as they relate to knockout non-human animal.

Claim Objections

Claim 1 can be more clearly written as a transgenic non-human animal whose somatic cells and germ cells are homozygous for a non-functional agouti-related protein (AgRP) gene (or "...for a disruption in the agouti-related protein (AgRP) gene").

Claim 2 can be more clearly written as "The transgenic non-human animal of claim 1, wherein the animal is a mouse, and further wherein said mouse exhibits reduced daytime respiratory quotient."

Claim 10, step e, should be "transplanting the injected blastocysts into a female mouse" to be more clear.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-7,10 and 19 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility.

Claim 1 is directed toward a transgenic non-human animal whose somatic and germ cells are homozygous for an altered AgRP gene which encodes a non-functional AgRP protein.

Claim 2 is directed toward the transgenic non-human animal of claim 1 wherein the animal is a mouse, and further wherein the mouse exhibits reduced daytime respiratory quotient.

Claim 4 is directed toward a transgenic mouse whose somatic cells are heterozygous for a functional AgRP protein and an altered AgRP gene.

Claim 6 is directed toward a transgenic mouse whose somatic cells are hemizygous for an altered AgRP gene.

The specification teaches making AgRP -/+ and -/- mice (pg 22-25, Example 1-3). AgRP is agouti related protein. "Mice homozygous for a null mutation do not exhibit any detectable abnormalities (see MGI webpage labeled "Gene Detail" for Agrp).

The specification taught AgRP -/- mice had decreased respiratory quotient (RQ) during the day but not at night (Fig. 18; pg 27, Example7). The specification does not teach how to use the mice to determine the role of AgRP in energy homeostasis. Furthermore, abnormal RQ is generic to 9 different gene disruptions in knockout mice (see MGI webpage labeled "Mammalian Phenotype Browser" for abnormal respiratory quotient). Therefore, the mice not have a use that is specific to the AgRP disruption because 9 other disruptions cause a related phenotype. It is noted that AgRP -/- mice are not listed as having abnormal RQ. Next, it is unclear how to use a mouse that only has decreased RQ during the day. Applicants provide no explanation for this anomaly, specifically as it relates to how to use the mouse. Finally, using the mice claimed to determine the role of AgRP within the realm of energy homeostasis is not a substantial use. Applicants have not described the pathways that affect energy homeostasis. Too

much "basic research" would be required to determine how the AgRP gene was involved in energy homeostasis. Applicants have merely provided a starting point for further research and not provided an end point of a research effort or by discussing the role of AgRP in energy homeostasis. Accordingly, applicants have not taught how to use the mice claimed as research tools for determining the role of AgRP in energy homeostasis.

Using the transgenics claimed to study the function of the AgRP gene is not a substantial utility. While the specification teaches using the mice in phenotype analyses and found homozygous mice had decreased RQ during the day (but not at night for some unexplained reason), the specification does not teach how to gain any more information about the function of the AgRP gene using the mice. Applicants have not taught any assays to study the function of the AgRP gene within the realm of energy homeostasis. Considering the number and complexity of pathways affecting energy homeostasis and the lack of teachings in the specification, applicants have not reasonable taught how to use the mice claimed to gain additional information about the function of the AgRP gene. The utility guidelines provide the meaning of a "well-established utility."

> A "well-known utility" is a specific, substantial and credible utility which is well know, immediately apparent, or implied by the specification's disclosure of the properties of the material, alone or taken with the knowledge of one skilled in the art. Neither a "well-established utility" nor a "specific utility" applies to any utility that one can dream up for an invention or a utility that would apply to virtually every member of a general class of materials, such as proteins or DNA.

The utility guidelines go on to describe a "substantial utility" and give examples of situations that fail to have a "real word" use.

> "[T]he following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":
> A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved."

Using the knockout mice to study the role of AgRP in energy homeostasis is basic research because it requires "further research" of the mouse itself. Therefore, such a use lacks substantial utility and consequently lacks a well-established utility. While scientists may have used knockout mice for basic research at the time of filing, basic research does not rise to the level of a "substantial," patentable utility. More importantly, applicants have not set forth the blaze marks for one of skill to conduct any "further research" so that one of skill would reasonably expect to determine the role of AgRP in energy homeostasis.

Using the transgenics claimed in expression analysis is not a substantial utility. Expression analysis revealed NPY expression was not significantly different in AgRP -/- mice while MCH expression was slightly elevated (pg 27, lines 7-17). The increase in MCH expression, however, may be compensation for AgRP deficiency (pg 27, lines 16-17). Using the knockout mice in "expression analysis" does not have substantial utility because it does not reveal the function of AgRP and does not allow those of skill to use the mice as "research tools."

Using the transgenics claimed as models of disease is not a substantial utility. The specification does not teach how to use such mice as models for disease, particular

as a model for energy homeostasis. The AgRP disruption does not correlate to a disruption found in humans with disease. The decreased RQ during the day does not correlate to a disease conditions found in humans. As such, the utility is not substantial.

Using the transgenics claimed to determine compounds that ameliorate a phenotype is not a specific or substantial utility because the specification does not teach how to determine compounds capable of treating disease. Specifically, the specification does not teach how to use the mice claimed to identify drugs that treat decreased RQ that occurs only during the day. In fact, merely administering a compound to the mouse made by applicants and observing whether RQ is improved is inadequate. The specification does not teach how to determine whether the compound is actually targeting AgRP or some other protein that affects energy homeostasis. The specification does not teach drugs targeting AgRP are capable of treating any cause of decreased RQ. For example, if AgRP protein functions only in one pathway that is related to energy homeostasis, drugs that target the AgRP protein would not ameliorate decreased RQ caused by disruptions in other proteins in the same pathway or in other pathways that do not require the AgRP protein. That would leave those skilled in the art with too much "further research" to use the mice claimed for identifying compounds that ameliorate decreased RQ that occurs only during the day because applicants have not even taught what pathway the protein functions in energy homeostasis. Finally, the specification does not teach how to make decisions about compounds that are administered to the mice claimed by teaching the specific controls used or when a compound is actually targeting the AgRP gene. Applicants have not taught the specific

steps required to decide whether a compound is actually targeting AgRP and not some other gene that affects development, whether the desire is to identify drugs that agonize or antagonize AgRP or that compounds targeting AgRP are capable of ameliorating decreased RQ in humans caused by other gene disruptions. Therefore, using the mice to identify compounds that ameliorate decreased RQ that only occurs during the day is so general as to be meaningless. As such, applicants have merely provided a starting point for further research without providing any blaze marks for using the mouse to study the role of the AgRP gene in energy homeostasis. Applicants have not provided an end point of a research effort by providing a compound that targets AgRP capable of treating decreased RQ or the specific steps required to do so.

Overall, the knockout mice do not correlate to "research tools" known to have patentable utility. For example, gas chromatographs separate the chemical components of a compound and identify them. Screening assays have various functions, but may be used, for example, to determine the amount of protein expression in a population of cells. Sequencing methods provide the nucleotide sequence of a nucleic acid molecule. Unlike gas chromatographs, screening assays or sequencing methods, the mice claimed are capable of providing data, but the may not reveal the function of the gene or provide any substantially useful information. Applicants used the mice of the invention in expression, phenotypic and behavioral analyses without determining the function of the AgRP gene, correlating the phenotype to a disease or identifying agents that alter the phenotype of the mice capable of treating disease. Further research would be required to determine the function of the AgRP gene, how to

use the mouse as a model of disease or to identify agents capable of treating disease. The utility guidelines state using a product for further research is not a "substantial" utility. In this case, the expression analysis and phenotype analyses merely provide a clue that the AgRP gene is related to embryonic lethality prior to implantation and decreased thermal nociception threshold. Applicants do not teach how to use the mouse claimed as a research tool to study the function of AgRP within those divergent fields.

As a final matter, the phenotype of AgRP knockout mice varies and is dependent upon what part of the AgRP is deleted (Miura, Transgenic Res., 2003, Vol. 12, pg 131-133). Miura taught some AgRP disruptions caused viable mice while others were lethal (see entire article). Qian (cited above), on the other hand, and the MGI webpage taught mice homozygous for a null mutation in the Agrp gene do not exhibit any detectable abnormalities.

In conclusion, merely using the transgenics claimed to obtain a clue that the AgRP gene is involved in energy homeostasis is the starting point for further research and fails to rise to the level of a patentable utility. Applicants have not revealed the function of the AgRP gene within the realm of energy homeostasis or provided the blaze marks to do so. Therefore, applicants have not provided adequate guidance for those of skill to use the transgenics claimed as research tools to study the role of AgRP within the realm of energy homeostasis.

The cells of claims 3, 5 and 7 lack patentable utility because the specification does not teach any use for cell lines derived from the transgenics as claimed and

because the transgenics from which the cells are derived do not have a patentable utility.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 10 and 19 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The specification does not enable making any transgenic non-human animal as broadly claimed. Claim 1 encompasses any transgenic non-human animal species. Claim 4 requires a mouse having a functional "murine" gene and an altered AgRP gene. "Murine" encompasses any rat or mouse gene (see Merriam-Webster Online definition of "murine"). Therefore, claim 4 encompasses a mouse having a functional rat or mouse gene, which does not make sense. The specification does not teach how to make or use any knockout non-human animal other than a mouse. The state of the art at the time of filing was such that embryonic stem (ES) cell technology had only been successful in mice. Wagner (May 1995, Clin. and Experimental Hypertension, Vol. 17, pages 593-605) and Mullins (1996, J. Clin. Invest., Vol. 98, 1557-1560) taught germline transmission of ES cells has not been demonstrated in species other than mice and the growth of ES cells from species other than mice is unreliable. Wall (1996,

Theriogenology, Vol. 45, pg 57-68) taught transgene expression and the physiological result of such expression in livestock was not always accurately predicted in transgenic mice (pg 62, line 7). The specification fails to provide sufficient guidance to make transgenics other than mice by teaching obtaining ES cells in species other than mice. Therefore, claims 1 should be limited to a mouse.

The specification does not enable one of skill to obtain the decreased RQ observed in transgenic mice in other non-human species. The art at the time of filing taught the species-specific requirements for making transgenics were unpredictable. For example, one transgene could cause two different phenotypes in mice and rats. Mullins (1990, Nature, Vol. 344, pg 541-544) produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse Ren-2 renin transgene. Hammer (1990, Cell, Vol. 63, pg 1099-1112) describes spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human β_2-microglobulin transgenes. Both investigations were preceded by the failure to develop human disease-like symptoms in transgenic mice (Mullins, 1989, EMBO, Vol. 8, pg 4065-4072; Taurog, 1988, J. Immunol., Vol. 141, pg 4020-4023) expressing the same transgenes that successfully caused the desired symptoms in transgenic rats. Furthermore, Ebert (1988, Mol. Endocrinology, Vol. 2, pages 277-283) taught a transgene encoding the human somatotropin gene operably linked to the mouse metallothionein promoter caused different phenotypes in transgenic pigs and mice (pg 277, col. 2, lines 17-27). Therefore, it was unpredictable whether the decreased RQ observed by applicants in

mice would occur in transgenic rat, pigs or any other non-human animal as broadly claimed.

The specification does not provide adequate guidance for those of skill to use the transgenics claimed. In particular, the specification taught AgRP -/- mice had decreased respiratory quotient (RQ) during the day but not at night (Fig. 18; pg 27, Example 7). The specification does not teach how to use the mice to determine the role of AgRP in energy homeostasis. It is unclear how to use a mouse that only has decreased RQ during the day. Applicants provide no explanation for this anomaly, specifically as it relates to how to use the mouse. The specification does not teach one assay for those of skill to use the transgenics claimed to determine the role of AgRP within the realm of energy homeostasis.

Claim 19 requires using the transgenics claimed to determine compounds that energy expenditure/utilization. However, the specification does not teach how to use the transgenics claimed to determine compounds capable of treating disease, specifically compounds capable of treating decreased RQ that occurs only during the day. Merely administering a compound to the mouse as in claim 2 and observing whether RQ is improved is inadequate. The specification does not teach how to determine whether the compound is actually targeting AgRP or some other protein that affects energy homeostasis. The specification does not teach drugs targeting AgRP are capable of treating any cause of decreased RQ. For example, if AgRP protein functions only in one pathway that is related to energy homeostasis, drugs that target the AgRP protein would not ameliorate decreased RQ caused by disruptions in other proteins in

the same pathway or in other pathways that do not require the AgRP protein. That would leave those skilled in the art with undue experimentation to use the transgenic mice to identify compounds that affect energy expenditure/utilization. The specification does not teach how to make decisions about compounds that are administered to the mice claimed by teaching the specific controls used or when a compound is actually targeting the AgRP gene. Applicants have not taught the specific steps required to decide whether a compound is actually targeting AgRP and not some other gene that affects development, whether the desire is to identify drugs that agonize or antagonize AgRP or that compounds targeting AgRP are capable of ameliorating decreased RQ in humans caused by other gene disruptions. Therefore, the specification does not enable using the transgenic mice to identify compounds that effect energy

The specification does not enable making a transgenic encoding any "non-functional AgRP protein" (claim 1) or any "altered AgRP gene" (claims 4, 6, 10) as broadly claimed. Claims 4 and 6 encompass transgenics expressing functional altered AgRP genes; however, the specification does not teach how to make or use any alterations in the AgRP gene that result in functional AgRP. Therefore, the claims should be limited to transgenics having a disruption in the AgRP gene or encoding a non-functional AgRP. In addition, the phenotype of AgRP knockout mice varies and is dependent upon what part of the AgRP is deleted (Miura, Transgenic Res., 2003, Vol. 12, pg 131-133). Miura taught some AgRP disruptions caused viable mice while others were lethal (see entire article). The specification does not teach how to use a

transgenic having an altered AgRP that dies in utero. Accordingly, the specification does not enable using a transgenic having any altered AgRP gene as broadly claimed.

The specification does not enable obtaining a hemizygote for an altered AgRP gene (claim 6) because the AgRP is not on the X chromosome and because the specification does not teach how to obtain an unpaired altered AgRP allele otherwise. A transgenic having one functional AgRP allele and one non-functional AgRP allele is a heterozygote, not a hemizygote.

The cells of claims 3, 5 and 7 are not enabled because the specification does not teach how to use cell lines derived from the transgenics as claimed and because the transgenics from which the cells are derived are not enabled.

Indefiniteness

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "the embryo" in claim 10, step f, lacks antecedent basis.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Kaelin (Society for Neurosci., Nov. 4-9, 2000, Vol. 26, No. 1-2, pg 125, Abstract 49.13) as supported by Kaelin (Endocrinology, Dec. 2004, Vol. 145, No. 12, pg 5798-5806).

Kaelin taught two transgenic mice having different targeting cassettes inserted into the AgRP gene. The AgRP gene comprising the targeting cassette "encodes a non-functional AgRP protein" as claimed because the targeting cassette was inserted between the coding and non-coding region and "did not recapitulate AgRP expression." Kaelin (2004) confirms the mice made had somatic cells and germ cells heterozygous and homozygous for the altered AgRP gene (pg 5799, "Materials and Methods").

Claims 1, 2, 4, 6, 10 and 19 are rejected under 35 U.S.C. 102(a) as being anticipated by Qian (Mol. Cell. Biol., 2002, Vol. 22, No. 14, pg 5027-5035, available online on June 20, 2002).

Qian was available online on June 20, 2002. See the fax from Linda M. Illig, Director of Journals for the American Society for Microbiology.

Qian taught mice whose somatic cells and germ cells comprised a heterozygous or homozygous disruption in the AgRP gene. The mice were made using the steps in claim 10 (pg 5028, col. 1, "Generation of Agrp -/- mice"). The mice of Qian inherently exhibited reduced daytime respiratory quotient (claim 2) because they have the same structure claimed, i.e. they do not express AgRP. The mice were given a high-fat diet, which is a "candidate compound" in claim 19, and appetite behavior and plasma leptin,

insulin levels were measured which is "measuring... ...expenditure and/or utilization of energy" in claim 19.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Weingarth, Soc. Neurosci. Abstract. 2002. Vol. 2002. Abstract # 134.

Wilson, Mol. Med. Today. June 1999. Vol. 5. No. 6. pg 250-256.

Barsh, Annals NY Acad. Sci. October 20, 1999. Vol. 885. pg 143-152.

Millhauser, Ann. NY Acad. Sci. June 2003. Vol. 994. pg 27-35.

Dinulescu, J. Biol. Chem. March 10 2000. Vol. 275. No. 10. pg 6695-6698.

Oilmann, Science, 10/03/97, Vol. 278, No. 5335, pg 135-139.

Erickson, Nature, Vol. 381, May 30, 1996, pg 415-418.

Salton, Neuron, February 2000, Vol. 25, pg 265-268, describes the numerous pathways that regulate energy homeostasis.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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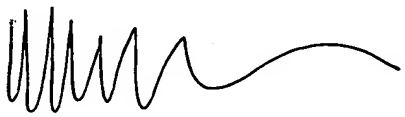
If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on 571-272-0735.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson



MICHAEL WILSON
PRIMARY EXAMINER